PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
RJW/6282743		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/000768	01.03.2005	01.03.2004

International Patent Classification (IPC) or national classification and IPC
C07D487/04, C07D519/00, A61K31/5517, A61P35/00

Applicant
SPIROGEN LIMITED

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 8 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23.12.2005	01.03.2006

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2005/000768

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-74	as originally filed

Claims, Numbers

1-10	as originally filed
11-34	received on 23.12.2005 with letter of 22.12.2005

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2005/000768

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 23

because:

☒ the said international application, or the said claims Nos. 23 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2005/000768

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10,24-34
	No:	Claims	11-23
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-34
Industrial applicability (IA)	Yes:	Claims	1-22, 24-34
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Due to the term "prodrugs" the present claims 11-20 encompass so many known compounds that it was not possible to cite all documents relevant to the issue of novelty. Therefore only some exemplary documents have been cited.

Claim 23 relates to subject matter considered by this Authority to be covered by the provisions of rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims (article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents have been cited in the International Search Report:

D1: CHEN ET AL: "A novel approach to the synthesis of cytotoxic C2?C3 unsaturated pyrrolo[2,1-c][and]benzodiazepines (PBDs) with conjugated acrylyl C2-substituents" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 14, no. 6, 27 February 2004 (2004-02-27), pages 1547-1550, XP002329273

D2: KANG ET AL: "Synthesis of a novel C2-aryl substituted 1,2-unsaturated pyrrolobenzodiazepine" CHEMICAL COMMUNICATIONS, vol. 14, 11 June 2003 (2003-06-11), pages 1688-1689, XP002329274

D3: GREGSON ET AL: "Synthesis of the first examples of A-C8/C-C2 amide-Linked pyrrolo[2,1-c][1,4]benzodiazepine dimers" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 13, no. 14, 31 March 2003 (2003-03-31), pages 2277-2280, XP002329063

D4: COOPER ET AL: "Synthesis of novel C2-aryl pyrrolobenzodiazepines (PBDs) as potential antitumour agents" CHEMICAL COMMUNICATIONS, vol. 16, 5 July 2002

(2002-07-05), pages 1764-1765, XP002329275

D5: GREGSON ET AL: "Synthesis of the first example of a c2-C3/C2?-C3?-endo unsaturated pyrrolo[2,1-c][1,4]benzodiazepine dimer" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 11, no. 21, 27 August 2001 (2001-08-27), pages 2859-2862, XP002329276

D6: GREGSON ET AL: "Effect of C2/C3-endo unsaturation on the cytotoxicity and dna-binding reactivity of pyrrolo[2,1-c][1,4]benzodiazepines" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 10, no. 16, 14 April 2000 (2000-04-14), pages 1849-1852, XP004216014

D7: WO 00/12508 A (THE UNIVERSITY OF PORTSMOUTH HIGHER EDUCATION (GB)) 9 March 2000 (2000-03-09)

D8: FUKUYAMA ET AL: "Total synthesis of (+)-porothramycin B" TETRAHEDRON LETTERS, vol. 34, no. 16, 16 April 1993 (1993-04-16), pages 2577-2580, XP002135999

Novelty (Article 33(2) PCT)

D1 to D8 disclose compounds which are potential "prodrugs" of the compounds of formula III and are therefore within the scope of claims 11-20. The matter of claims 11 to 23 is therefore not novel.

The Applicant allges in his letter of 22.12.2005 that the compounds of claims 11 and 14 differ from the prior art compounds in that both the N10 and C11 hydroxy positions are protected.

This is not correct, the hydroxy "unprotected" prior art compounds are potential "prodrugs" of the compounds of present formula III, since they will be transformed in-vivo to their e.g. acyl derivatives.

The compounds of claim 1 differ from the compounds in D1 in the oxygen protecting group

R11 (claim 1 does not encompass "prodrugs" since they are intermediates and not active principles). Claims 1-10 and 24-34 are therefore novel.

Inventive Step (Article 33(3) PCT)

The problem of claims 1-10 and 24-34 was the provision of a new process and new intermediates for the preparation of compounds of claim 11. D1 could be regarded as the closest prior art.

The present process of claim 31 and the present intermediates of claim 1 are analogous to the process and intermediates which have already been disclosed in D1. The present intermediates differ only in the use of an oxygen-protecting group R11. The use of oxygen-protecting groups is an obvious measure for a skilled person.

Therefore the present claims 1-10 and 24-34 lack an inventive step.

The problem of claims 11-23 was the provision of new compounds for the treatment of proliferative diseases. D1 could be regarded as the closest prior art. Since the compounds as well as their pharmacology are well known from D1-D8, the matter of claims 11-23 also lacks an inventive step.

New compounds of claims 11-23 might differ from structurally related prior art compounds in D1-D8 in that both the N10 and C11 hydroxy positions are protected. The provision of hydroxy protected derivatives of known pharmacologically active compounds is not regarded as an activity based on an inventive step.

The Applicant argues in his letter of 22.12.2005 that the present C11 hydroxy protected intermediates have an advantage when compared with the compounds in D1, which are C11 hydroxy "unprotected", since such intermediates can be used in a wider range of synthesis, e.g. of Stille and Suzuki coupling, for preparing a wider range of C2-derivatives.

This is true, but the use of hydroxy protecting groups in reactions which are known to be incompatible with a free hydroxy group is an obvious measure for a skilled person.

The Applicant further argues that the compounds of claim 14 are inventive over the structurally closest related compounds in D5 because the C2 aryl substituent. The Applicant provides data which show an increased activity of a C2 aryl substituted test compound when compared to a C2 unsubstituted reference compound of D5. The first problem is that the test compound is not a compound according to the present invention, since it is unsubstituted at the N10 and C11 positions and has a N10=C11 double bond. The second problem is that a unitary group of inventions must have a common inventive concept, i.e. a common distinctive feature. According to the Applicant this special technical feature is the C11 protective group. In order to establish an inventive step, the Applicant should have made credible by means of comparative data, that this C11 protective group has an effect on the pharmacological activity of the final compounds.

Re Item VI

Certain documents cited

Reference is made to the following P-documents:

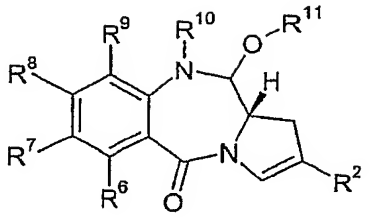
D9: WO 2004/043963 A (SPIROGEN (GB)) 27 May 2004 (2004-05-27)

D10: TIBERGHIEN ET AL: "Application of the Stille coupling reaction to the synthesis of C2-substituted endo-exo unsaturated pyrrolo[2,1-c][1,4]benzodiazepines (PBDs)" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 14, no. 20, 1 September 2004 (2004-09-01), pages 5041-5044, XP002329277

The priority documents pertaining to the present application were not available at the time of establishing this report. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, D9 and D10 could become relevant to asses whether the present claims satisfy the criteria set forth in Article 33(1) PCT.

CLAIMS

1. A compound of formula I:



I

and salts, solvates and chemically protected forms thereof, wherein:

R^6 and R^9 are independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', nitro, Me_3Sn and halo;

R and R' are independently selected from optionally substituted C_{1-12} alkyl, C_{3-20} heterocyclyl and C_{5-20} aryl groups;

R^7 and R^8 are independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', nitro, Me_3Sn and halo,

or the compound is a dimer with each monomer being of formula (I), where the R^7 groups or R^8 groups of each monomers form together a dimer bridge having the formula -X-R"-X- linking the monomers, where R" is a C_{3-12} alkylene group, which chain may be interrupted by one or more heteroatoms and/or aromatic rings, and each X is independently selected from O, S, or NH;

or any pair of adjacent groups from R^6 to R^9 together form a group -O-$(CH_2)_p$-O-, where p is 1 or 2;

R^{10} is a carbamate-based nitrogen protecting group;

R^{11} is an oxygen protecting group; and

R^2 is a labile leaving group.

2. A compound according to claim 1, wherein R^9 is H.

3. A compound according to either claim 1 or claim 2, wherein R^6 is selected from H, OH, OR, SH, NH_2, nitro and halo.

4. A compound according to any one of the preceding claims, wherein R^{10} is Troc.

5. A compound according to any one of the preceding claims, wherein R^{11} is a silyl oxygen protecting group or THP.

6. A compound according to any one of the preceding claims, wherein R^2 is triflate.

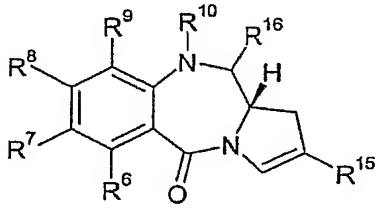
7. A compound according to any one of the preceding claims, wherein R^7 and R^8 are independently selected from H, OH, OR, SH, NH_2, NHR, NRR' and halo.

8. A compound according to any one of claims 1 to 6, wherein the compound is a dimer with each monomer being of formula (I), where the R^7 groups or R^8 groups of each monomer form together a dimer bridge having the formula $-O-(CH_2)_n-O-$ linking the monomers, where n is from 3 to 12.

9. A compound according to claim 8, wherein n is from 3 to 7.

10. A compound according to either claim 8 or claim 9, wherein the substituents R^8 join to form the dimer bridge.

11. A compound of formula **III**:



III

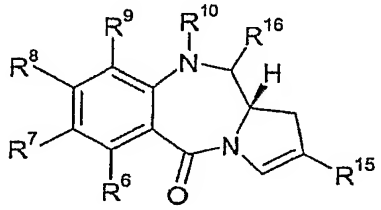
and salts, solvates, chemically protected forms and prodrugs thereof, wherein:
R^6 and R^9 are independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', nitro, Me_3Sn and halo;
R and R' are independently selected from optionally substituted C_{1-12} alkyl, C_{3-20} heterocyclyl and C_{5-20} aryl groups;
R^7 and R^8 are independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', nitro, Me_3Sn and halo,

or any pair of adjacent groups from R^6 to R^9 together form a group $-O-(CH_2)_p-O-$, where p is 1 or 2;
R^{10} is a carbamate-based nitrogen protecting group; and
R^{16} is $O-R^{11}$, wherein R^{11} is an oxygen protecting group,
and R^{15} is R.

12. A compound according to claim 11, wherein when R^7 and R^8 are OMe, R^6 and R^9 are H, and R^{15} is R, R is selected from the group 3-methoxyphenyl, 4-biphenyl, 4-phenoxyphenyl, 3,4-methylenedioxyphenyl, trans-2-(4-methylphenyl)vinyl, trans-propenyl, 4-dimethylaminophenyl, 4-methylthiophenyl, 4-vinylphenyl, 3,4-dichlorophenyl, 4-trifluoromethylphenyl, 4-isopropylphenyl, 4-cyanophenyl, 3-pyridinyl, 4-pyridinyl, 4-formylphenyl, 4-carboxylphenyl, 2,6-dimethoxyphenyl, 4-acetanilide, 4-aminophenyl, 1-naphthyl, 5-indole, 3-aminophenyl, 2,6-difluorophenyl, 1-pyrenyl, 4-hydroxyphenyl and trans-hexenyl.

13. A compound according to either claim 11 or claim 12, wherein when R^7 and R^8 are OMe, R^6 and R^9 are H, and R^{15} is R, R is selected from a C_{3-20} heterocyclyl group having a nitrogen ring atom, C_{5-20} aryl group having a nitrogen-containing substituent, or a C_{5-20} heteroaryl group having a nitrogen ring atom or a nitrogen-containing substituent.

14. A compound of formula **III**:



III

and salts, solvates, chemically protected forms and prodrugs thereof, wherein:
R^6 and R^9 are independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', nitro, Me_3Sn and halo;
R and R' are independently selected from optionally substituted C_{1-12} alkyl, C_{3-20} heterocyclyl and C_{5-20} aryl groups;

the compound is a dimer with each monomer being of formula (I), where the R^8 groups of each monomer form together a dimer bridge having the formula -X-R"-X- linking the monomers, where R" is a C_{3-12} alkylene group, which chain may be interrupted by one or more heteroatoms and/or aromatic rings, and each X is independently selected from O, S, or NH, and R^7 is selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', nitro, Me_3Sn and halo,
or any pair of adjacent groups from R^6 to R^9 together form a group $-O-(CH_2)_p-O-$, where p is 1 or 2;
R^{10} is a carbamate-based nitrogen protecting group; and
R^{16} is $O-R^{11}$, wherein R^{11} is an oxygen protecting group, and R^{15} is an optionally substituted C_{5-20} aryl group.

15. A compound according to claim 14, wherein the dimer bridge has the formula $-O-(CH_2)_n-O-$ linking the monomers, where n is from 3 to 12.

16. A compound according to claim 15, wherein n is from 3 to 7.

17. A compound according to any one of claims 14 to 16, wherein R^{10} and R^{16} together form a double bond between N10 and C11.

18. A compound according to any one of claims 11 to 17, wherein R^9 is H.

19. A compound according to any one of claims 11 to 18, wherein R^7 and R^8 are independently selected from H, OH, OR, SH, NH_2, NHR, NRR' and halo.

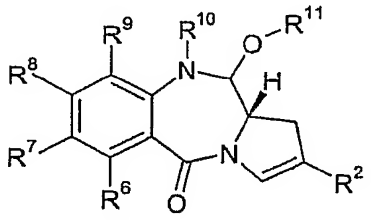
20. A compound according to any one of claims 11 to 19 for use in a method of therapy.

21. A pharmaceutical composition containing a compound of any one of claims 11 to 19, and a pharmaceutically acceptable carrier or diluent.

22. Use of a compound according to any one of claims 11 to 19 in the manufacture of a medicament for treating a proliferative disease.

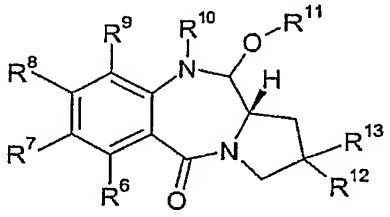
23. A method of treatment of a proliferative disease, comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound of any one of claims 11 to 19.

24. A method of synthesising a compound of formula **I**:



I

from a compound of formula **IIa**:



IIa

wherein:

R^6 and R^9 are independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR′, nitro, Me_3Sn and halo;

R and R′ are independently selected from optionally substituted C_{1-12} alkyl, C_{3-20} heterocyclyl and C_{5-20} aryl groups;

R^7 and R^8 are independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR′, nitro, Me_3Sn and halo,

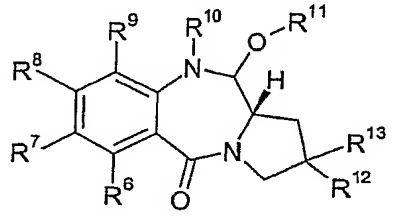
or the compound is a dimer with each monomer being of formula (**I**), where the R^7 groups or R^8 groups of each monomers form together a dimer bridge having the formula -X-R″-X- linking the monomers, where R″ is a C_{3-12} alkylene group, which chain may be interrupted by one or more heteroatoms and/or aromatic rings, and each X is independently selected from O, S, or NH;

or any pair of adjacent groups from R^6 to R^9 together form a group -O-$(CH_2)_p$-O-, where p is 1 or 2;

R^{10} is a carbamate-based nitrogen protecting group;

R^{11} is an oxygen protecting group;
R^2 is a labile leaving group; and
R^{12} and R^{13} together form =O.

25. A method according to claim 24, wherein the compound of formula **IIa** is synthesised from a compound of formula **IIb**:



IIb

wherein said compound of formula **IIb** has R^6, R^7, R^8, R^9, R^{10} and R^{11} defined according to claim 25, and for said compound of formula **IIb** R^{12} is O-R^{14}, and R^{13} is H; and
R^{14} is an oxygen protecting group orthogonal to R^{11}.

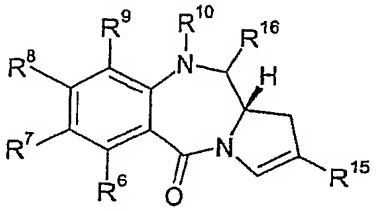
26. A method according to claim 25, wherein the compound of formula **IIa** is synthesised using an oxidation reaction performed under Swern conditions, or a method involving the TPAP or the Dess Martin reagents.

27. A method according to any one of claims 24 to 26, wherein when R^2 in the compound of formula **I** is $-OSO_2CH_3$, $-OSO_2(C_nF_{2n+1})$ where n = 0, 1 or 4, or $-OSO_2R^S$ where R^S is an optionally substituted phenyl group, then said compound of formula **I** is synthesised by using a treatment step with the appropriate R^2 anhydride.

28. A method according to any one of claims 24 to 26, wherein when R^2 in the compound of formula **I** is -I or -Br, then said compound of formula **I** is synthesised by using a reaction step involving hydrazine and iodine or bromine.

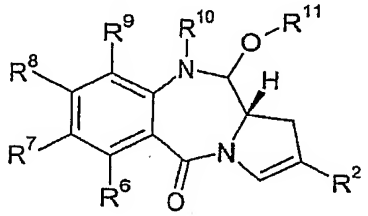
29. A method according to any one of claims 24 to 26, wherein when R^2 in the compound of formula **I** is -Cl, then said compound of formula **I** is synthesised by using a reaction step involving phosphorous oxychloride.

30. A method of synthesising a compound of formula **III**:



III

from a compound of formula **I**:



I

wherein

R^6 and R^9 are independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', nitro, Me_3Sn and halo;

R and R' are independently selected from optionally substituted C_{1-12} alkyl, C_{3-20} heterocyclyl and C_{5-20} aryl groups;

R^7 and R^8 are independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', nitro, Me_3Sn and halo,

or the compound is a dimer with each monomer being of formula (I), where the R^7 groups or R^8 groups of each monomers form together a dimer bridge having the formula -X-R"-X- linking the monomers, where R" is a C_{3-12} alkylene group, which chain may be interrupted by one or more heteroatoms and/or aromatic rings, and each X is independently selected from O, S, or NH;

or any pair of adjacent groups from R^6 to R^9 together form a group $-O-(CH_2)_p-O-$, where p is 1 or 2;

R^{10} is a carbamate-based nitrogen protecting group;

R^2 is a labile leaving group;

R^{16} is either $O-R^{11}$, where R^{11} is an oxygen protecting group, or OH, or R^{10} and R^{16} together form a double bond between N10 and C11; and

R^{15} is R.

31. A method according to claim 30, wherein the synthesis of said compound of formula **III** uses a palladium catalysed coupling step.

32. A method according to claim 31, wherein the palladium catalyst is $Pd(PPh_3)_4$, $Pd(OCOCH_3)_2$, $PdCl_2$ or $Pd(dba)_3$.

33. A method according to either claim 31 or claim 32, wherein the coupling reaction is performed under microwave conditions.

34. A method according to any one of claims 31 to 33, wherein the palladium catalyst is solid supported.